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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
LOEB, B	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/392,682	Applicant(s) GRUENERT ET AL.	
	Examiner Bronwen M. Loeb	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This action is in response to the amendment filed July 3, 2001 in which claims 8-16 were cancelled and new claims 17-40 were submitted.

Any rejection from any previous action not repeated herein has been withdrawn.

Claims 17-40 are pending.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 17, 20-26, and 28-36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9, 10 and 12 of U.S. Patent No. 6,010,908. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the pending application are generic compared to the claims in USP 6,010,908. For instance, all of the elements recited in pending claim 17 (delivering an exogenous replacement DNA fragment to a cell wherein the fragment consists at least one replacement exon and flanked by

intronic sequences which are homologous to the flanking sequences in the target gene) are also recited in claim 1 of USP 6,010,908; claim 1 of USP 6,010,908 recites additional elements making the scope of that claim narrower than the pending claim. A species claim renders a genus obvious.

Claim Objections

3. Claim 21 is objected to because of the following informalities: "cell" is misspelled in line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 18, 19 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 18 encompasses the method of replacing a target fragment in a cell wherein the cell is ex vivo. Claim 19 encompasses the method of replacing a target fragement in a cell wherein the cell is in vivo. Claim 38 encompasses a method for gene therapy wherein a replacement fragment is delivered into a cell and corrects a genetic defect.

The nature of the invention is a method of treatment by replacing a target fragment in a gene associated with a disease with an exogenous replacement fragment which corrects the genetic defect in the disease-asociated gene. The delivery of nucleic acid in vivo or ex vivo for therapeutic purposes constitutes gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and

col. 1, 1st and 2nd paragraphs. While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al , p. 33, col. 1, 1st paragraph.

The relative skill of those in the art of gene therapy and homologous recombination is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, particularly low efficiency of delivery of the nucleic acid. There is no direction on how to ensure that cells from the ex vivo method would replace, or otherwise out-compete, the endogenous defective cells.

There are no working examples disclosed which encompass in vivo or ex vivo applications of the claimed methods.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency and how to obtain a sufficient level of homologous recombination in the target cells to achieve a level which would provide sufficient expression to induce at least some therapeutic effect. If the targeted genetic defect is a dominant negative, one would have to further determine how to ensure replacement of both copies (assuming a single locus gene) of the defective exon. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method of ex vivo or in vivo gene therapy for replacing a target fragment using homologous recombination.

6. Claims 17 and 20-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for replacing a target fragment in a cell in vitro, does not reasonably provide enablement for a method of replacing a target fragment in vivo or ex vivo, wherein the cells are intended for gene therapy use. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection is based on the same reasons discussed in the full enablement rejection preceding this rejection.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 20-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is vague and indefinite as it is unclear what the phrase "a genetic defect that controls a disease or dysfunction" means. Does it mean that the defect controls the progression or severity of a disease? Does it mean that it is the underlying cause of a disease or a dysfunction?

Claim 22 recites the limitation "the target fragment of a gene" in line 1. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "the target fragment of the gene" as recited in claim 20.

Claim 23 recites the limitation "the target fragment of a gene" in line 1. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "the target fragment of the gene" as recited in claim 20.

Claim 23 is vague and indefinite as it recites "a replacement genomic DNA sequence encoding β globin". This recitation is claiming a whole β globin gene. Is this replacement fragment consistent with the recitation in claim 17, upon which this claim depends?

Claim 24 recites the limitation "the targeted mutant DNA sequence" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 25 recites the limitation "the targeted mutant DNA sequence" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 26 is vague and indefinite as it is unclear to which DNA recited in claim 17 the phrase "the DNA" refers.

Claim 27 is vague and indefinite as it is unclear to which DNA recited in claim 17 the phrase "the DNA" refers.

Claim 29 is vague and indefinite in reciting "the method is directed at a population of cells containing the target fragment of the gene". It is unclear if this is meant to be an additional method step and if so, how it is carried out.

Claim 29 recites the limitation "the target fragment of a gene" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "the target fragment of the gene".

Claim 30 recites the limitation "the target fragment of a gene" in line 4. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "the target fragment of the gene".

Claim 30 is vague and indefinite. Claim 30 recites three specific ways of identifying the exogenous replacement DNA fragment in cells; the first two specify features of the primers used for PCR. The third way is by Southern hybridization. Claim 30 is dependent on claim 29, which recites the step of "determining the extent of homologous replacement by PCR identification". Southern hybridization is not a PCR method, but rather an alternative to PCR identification of recombinant cells.

Claim 35 is vague and indefinite as it recites "a replacement genomic DNA sequence encoding β globin". This recitation is claiming a whole β globin gene. Is this replacement fragment consistent with the recitation in claim 17, upon which this claim depends?

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Regarding claims 17-37, the phrase "consisting essentially of" with respect to DNA has been interpreted as open language in the absence of a definition in the specification. Additional sequence is encompassed by such claims as long as such additional sequence does not change the basic nature of the invention.

11. Claims 17-20, 27-30, 32 and 37-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Berns et al (USP 5,789,215). Berns et al teaches a method for modifying the genome of an animal cell by delivering a targeting DNA molecule having desired sequence modifications in a segment of DNA which is isogenic with the target DNA in the genome to the cell and wherein homologous recombination yields the modified genome. The method may be done ex vivo or in vivo. The delivery methods include electroporation and transfection. The method may be used to correct a defective gene and can target an exon. In example I, their targeting DNA molecule, a double stranded DNA molecule obtained by restriction enzyme cleavage of a plasmid, comprises the 19th and 20th exons of the retinoblastoma gene and adjacent sequence (i.e. intronic sequences). Recombinant cells may be identified by PCR or by Southern hybridization analysis. See entire document.

12. Claims 17-20, 26-29, 31 and 37-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Vega (Human Genetics (1991) 87:245-253). Vega teaches a method of gene therapy based on the use of homologous recombination using linear double stranded or single stranded DNA fragments derived from genomic DNA covering the mutation in a particular gene. Although the fragment need only cover the mutation and have flanking sequences homologous to the targeted DNA, it can encompass the whole gene, for instance to correct regulatory defects in unexpressed sequence. As a consequence, the replacement fragment may comprise at least one exon and 5' and 3' flanking intronic sequences. The replacement fragment may be associated with recombination active proteins to improve efficiency of targeting. Deliver means taught

include microinjection. Ex vivo and in vivo approaches are taught. See entire document.

13. Claims 17, 20, 21, 23, 27-30, 32 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Shesely et al (Proc. Natl. Acad. Sci. USA (1991) 88:4294-4298). Shesely et teach a method of replacing a defective β^S-globin gene which causes sickle cell disease, with the normal β^A-globin allele. The targeting construct is from genomic DNA and therefore comprises at least one exon and 5' and 3' flanking intronic sequences homologous to the defective target gene. It is a double-stranded fragment cut out of a plasmid and is electroporated into the target cell. The extent of homologous replacement is determined by Southern hybridization and PCR. See entire document.

14. Claims 17, 18, 20-22, 27-32 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Kay et al (USP 5,612,205). Kay et al teach a method of homologous recombination in mammalian cells comprising the use of at least two fragments derived from genomic DNA sequence each having a region of homology with the other and which are co-transfected into the target cell. The at least two fragments recombine homologously to form a single DNA fragment which may then homologously recombine with the genomic target sequence. In Example 1, three fragments, each comprising at least one exon and flanking 5' and 3' intronic sequences, are microinjected into male pronuclei of fertilized mouse eggs wherein the three fragments homologously recombined with each other and with the endogenous albumin gene. Southern hybridization was used to assess the homologous recombination. The method may be used in ex vivo gene therapy approaches to correct genetic diseases

due to mutant cystic fibrosis or hemoglobin genes. The method must be used in recombination competent cells, that is, cells containing recombinases, endogenous or otherwise. See entire document, especially col. 3, lines 12-16, col. 6, lines 55-67, col. 8, lines 6-56, col. 10, lines 10-13 and col. 12, line 5- col. 13, line 6..

15. Claim 37 is rejected under 35 U.S.C. 102(b) as being anticipated by Tsui et al (WO 91/10734). Tsui et al teach generating specific exons from the cystic fibrosis gene using PCR and primers that anneal to the flanking intronic sequences. The result from such a PCR reaction is an aqueous composition comprising a DNA fragment comprising an exon with flanking 3' and 5' intronic sequences which are homologous to the specific corresponding intron sequences in the cystic fibrosis gene. See Figure 18 and pp. 64-66.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 17-20, 26-29, 31 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vega. Vega is applied as above. Vega does not teach that the replacement fragment is about 1 to about 2000 bases. At the time of the invention, it would have been obvious to one of ordinary skill in the art to use a fragment of less than 2000 bases. One of ordinary skill in the art would have been motivated to do so because Vega teaches that one of the advantages of gene targeting is that the fragment need not cover the whole gene, but rather only the mutation site and sufficient regions of homologous sequence on either side.

Conclusion

Claims 17-40 are rejected. Claims 24, 25 and 33-36 are free of prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

October 1, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER